

Comorbidities of Diabetes and Hypertension: Mechanisms and Approach to Target Organ Protection

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Up to 75% of adults with diabetes also have hypertension, and patients with hypertension alone often show evidence of insulin resistance. Thus, hypertension and diabetes are common, intertwined conditions that share a significant overlap in underlying risk factors (including ethnicity, familial, dyslipidemia, and lifestyle determinants) and complications. These complications include microvascular and macrovascular disorders. The macrovascular complications, which are well recognized in patients with longstanding diabetes or hypertension, include coronary artery disease, myocardial infarction, stroke, congestive heart failure, and peripheral vascular disease. Although microvascular complications (retinopathy, nephropathy, and neuropathy) are conventionally linked to hyperglycemia, studies have shown that hypertension constitutes an important risk factor, especially for nephropathy. The familial predisposition to diabetes and hypertension appears to be polygenic in origin, which militates against the feasibility of a "gene therapy"

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approach to the control or prevention of these conditions. On the other hand, the shared lifestyle factors in the etiology of hypertension and diabetes provide ample opportunity for nonpharmacologic intervention. Thus, the initial approach to the management of both diabetes and hypertension must emphasize weight control, physical activity, and dietary modification. Interestingly, lifestyle intervention is remarkably effective in the primary prevention of diabetes and hypertension. These principles also are pertinent to the prevention of downstream macrovascular complications of the two disorders. In addition to lifestyle modification, most patients will require specific medications to achieve national treatment goals for hypertension and diabetes. Management of hyperglycemia, hypertension, dyslipidemia, and the underlying hypercoagulable and proinflammatory states requires the use of multiple medications in combination. J Clin Hypertens (Greenwich). 2011;13:244–251. ©2011 Wiley Periodicals, Inc.

Hypertension and diabetes affect approximately 74.5 million and 23.6 million adults in the United States, respectively, and approximately 75% of patients with diabetes have concomitant hypertension.¹ Both conditions are also increasingly being recognized in adolescents and younger adults.^{1,2} The economic impact of hypertension and diabetes is an enormous burden on society, with an estimated annual cost of \$174 billion for diabetes care and \$76.6 billion for hypertension-related problems.^{1,2} There is a significant amount of overlap between the complications of diabetes and hypertension. These

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complications can be divided into macrovascular and microvascular disorders. Macrovascular complications include coronary artery disease, myocardial infarction, congestive heart failure, stroke, and peripheral vascular disease. Cardiovascular (CV) disease (CVD) is the leading cause of death in the United States, and both diabetes and hypertension are major CVD risk factors.^{1,2} The microvascular complications of diabetes include retinopathy, nephropathy, and neuropathy. The leading cause of noncongenital blindness is diabetes-related retinopathy, and that of end-stage renal disease is diabetic nephropathy.¹ In addition, foot ulcers and peripheral artery disease in diabetic patients account for two thirds of all nontraumatic amputations in the United States.¹ Hypertension also has a significant impact on the incidence and progression of CV events and microvascular complications. The macrovascular and microvascular complications of hypertension and diabetes overlap considerably and may share common mechanisms. The familial predisposition to diabetes and hypertension appears to be polygenic in origin, although specific genetic mechanisms modulating susceptibility or protection from these complications have yet to be identified.^{3,4} The polygenic origin and lack of precise knowledge at the molecular genomic and proteomic levels make it unrealistic to expect that a gene therapy approach would emerge as a practical option for the control or prevention of hypertension and diabetes. In the present review, we discuss the pathogenesis and clinical manifestations of microvascular and macrovascular complications associated with hypertension and diabetes and offer evidence-based strategies for primary prevention and optimal control of risk factors.

ROLE OF HYPERGLYCEMIA

The biochemical basis of diabetes microvascular complications is well established. Hyperglycemia-induced abnormalities in the polyol, hexosamine, and protein kinase C pathways have been shown to mediate tissue damage in diabetes.^{3,5,6} In addition, hyperglycemia promotes the formation of toxic advanced glycated end products and induces glomerular hyperfiltration, aberrant growth factor expression, and free radical damage from reactive oxygen species.⁷⁻¹³ The pathogenesis of macrovascular disease is multifactorial, with significant contributions from dyslipidemia, hypertension, hyperglycemia, insulin resistance, dysfibrinolysis, obesity, and lifestyle factors such as sedentary habits and smoking.¹⁴ The basic atherosclerosis processes leading to

coronary, cerebrovascular, or peripheral vascular disease are similar in all patients, but those with hypertension and diabetes appear to have accelerated development of advanced lesions.¹⁵ Studies have shown that the benefit of early glycemic control to reduce the future risk of microvascular and CV complications is sustained beyond the period of good glycemic control ("metabolic memory").^{16,17} The pathophysiologic link between hyperglycemia and macrovascular disease includes possibly direct effects of glucose, activation of protein kinase C, endothelial dysfunction from oxidative stress, activation of atheroinflammatory cytokines, and epigenetic changes, among others.^{18,19} The superimposition of hypertension on diabetes further aggravates microvascular and macrovascular complications through additive mechanisms that include arteriolar and capillary damage in retinal, renal, coronary, cerebral, and peripheral vascular territories. These added lesions accelerate the progression to target-organ renal failure.²⁰

MACROVASCULAR DISEASE

Diabetes increases the risk of CVD and stroke by 2 to 4 times that of nondiabetic persons.¹ The Multiple Risk Factor Intervention Trial (MRFIT) demonstrated an increased risk of CVD in persons with diabetes, even after adjusting for age and other CV risk factors, such as hypertension, smoking, and hypercholesterolemia.²¹ Both type 1 and type 2 diabetes are associated with a marked increase in CVD risk, which is amplified by the presence of multiple risk factors.²¹ In a prospective study conducted in Finland, the risk of coronary artery disease–related death was similar in patients with diabetes and no history of prior myocardial infarction compared with those without diabetes and prior myocardial infarction.²² This study provided the rationale for the popular classification of diabetes as a "coronary artery disease equivalent," a concept that has sometimes been questioned regarding its generalizability. Hypertension also increases the risk of CVD and stroke, the first and third leading causes of death in the United States, respectively.² In the Hypertension in Diabetes Study, patients with hypertension and concomitant diabetes compared with nonhypertensive diabetics were found to have higher rates of CV death, myocardial infarction, angina pectoris, amputation, and stroke independent of other risk factors.²³ Despite a decline in the rate of mortality from heart disease in the United States, there has been a less marked decline seen in persons with diabetes, especially women.²⁴

Furthermore, the contribution of peripheral vascular disease to the risk of lower extremity

amputation in patients with diabetic neuropathy is well-known.

The metabolic syndrome, often present for years before diabetes is diagnosed, clearly predisposes patients with type 2 diabetes to increased risk of CVD. Components of the metabolic syndrome include insulin resistance, upper body obesity, hyperinsulinemia, hypertriglyceridemia, increased small dense low-density lipoprotein cholesterol and decreased high-density lipoprotein cholesterol levels, hypertension, hyperuricemia, and a procoagulant state, among others.¹⁴ Endothelial dysfunction also tracks the severity of insulin resistance. Indeed, as demonstrated in the European Prospective Investigation of Cancer (EPIC)-Norfolk study, cardiometabolic risk factors can be associated with increased CVD events and mortality even during the prediabetes stage.^{14,25} Although insulin resistance is not a characteristic feature of type 1 diabetes, a phenotype of insulin resistance can be superimposed on pre-existing type 1 diabetes, particularly in persons with a family history of type 2 diabetes and those who develop abdominal obesity.¹⁴

MICROVASCULAR COMPLICATIONS

Diabetic retinopathy is responsible for 12,000 to 24,000 new cases of vision loss each year.¹ Coexistence of hypertensive retinopathy and diabetic retinopathy further magnifies the risk of vision loss.²⁶ In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), 14% of patients with type 1 and 33% with type 2 diabetes had developed diabetic retinopathy within 5 years of diagnosis of diabetes.²⁷ Diabetic retinopathy is generally classified as proliferative or nonproliferative. Nonproliferative diabetic retinopathy describes the pathologies of increased capillary permeability, hemorrhage, and macular edema, and may progress to proliferative retinopathy. The latter results from neovascularization on the vitreous surface of the retina, vitreous cavity, and the iris. Over time, scarring and fibrosis occurs, causing traction of the retina that can progress to retinal detachment and vision loss.

Diabetic nephropathy occurs in as many as 40% of patients with diabetes, and hypertension magnifies the risk of this microvascular complication.^{28,29} Diabetic nephropathy differs from other causes of renal disease at the histopathologic level. Initially, the glomerular basement membrane thickens, followed by an increase in the amount of mesangial matrix that in some patients can progress to increasingly more severe diffuse or nodular glomerulosclerosis.²⁸ The basement membrane may be gradually lost in diabetes mellitus, leading to loss of its sieve-like

permselectivity and progressive proteinuria.³⁰ This change in the basement membrane permselectivity appears to be caused by nonenzymatic glycosylation of long-lived proteins.³⁰ In addition, advanced glycosylation end products bind to mesangial cells and cause increased formation of fibronectin and basement membrane collagen.³¹ Overt diabetic nephropathy is characterized by urine albumin excretion >300 mg/24 hours, and is associated with a 1 mL/min/1.73 m² decline in glomerular filtration rate (GFR) per month. Microalbuminuria is an early indicator of diabetic nephropathy, and is also associated with an increased risk of CVD.³²

Diabetic peripheral neuropathy affects approximately 70% of diabetic patients and is the leading cause of foot amputation.¹ The pathogenesis of peripheral neuropathy is poorly understood but felt to be related to impaired blood flow, demyelination of nerves, and inflammation. However, it is also known that peripheral neuropathy develops in the background of long-standing hyperglycemia and its associated metabolic derangements: increased polyol flux, accumulation of advanced glycosylation end products, lipid derangements, and oxidative stress.³³ Hyperglycemic exposure appears to be the most important risk covariate, and rigorous glycemic control is recommended to stabilize and sometimes improve symptoms.³³

Autonomic neuropathy typically manifests as orthostatic hypotension, decline in vasomotor tone, anhidrosis, and pupillary abnormalities. However, patients may also have impairment in CV, gastrointestinal, and urogenital function. CV autonomic neuropathy can manifest as orthostatic hypotension, lack of normal heart rate variation with breathing, resting tachycardia, and even sudden death. The presence of autonomic neuropathy identifies patients at high risk for CVD and can be used for risk stratification independent of other CVD risk markers.³³ Risk factors associated with development of CV autonomic neuropathy include hyperglycemia, diabetic peripheral neuropathy, nephropathy and retinopathy, hypertension, obesity, smoking, and dyslipidemia.³³

INTERVENTIONS

Pharmacologic Targeting of Glycemic Control

Since hyperglycemia is the major catalyst in the pathogenesis of microvascular disease, optimization of glycemic control is an approach to primary prevention and of microvascular complications. Moreover, the chronologic evolution of microvascular complications allows for an effective policy of targeted screening and surveillance (Table I). A

Table I. Screening for Microvascular Complications			
COMPLICATION	METHOD	FREQUENCY	OPTIMAL GOALS
Nephropathy	Urine microalbumin	Annually ^a	Albumin <30 mg/24 h or albumin–creatinine ratio <30 mg/g in random urine specimen
	GFR estimation by serum creatinine	Annually	GFR >90 mL/min/1.72 m ²
Retinopathy	Dilated and comprehensive eye examination	Initially: type 1, 3–5 y after onset; type 2, from diagnosis Annually: more frequently if pregnant or progressive retinopathy	Primary prevention, delay of progression and prevention of blindness from retinopathy
Neuropathy	Daily self-inspection of feet	Every visit	Intact skin
	Comprehensive foot examination	Annually	Normal examination
	Examination for distal symmetric polyneuropathy	At diagnosis and annually	Early detection and limb preservation
	Assessment for autonomic neuropathy	Type 1: 5 years after diagnosis Type 2: from diagnosis	Early detection, symptom control, recognition of associated cardiovascular risk
Abbreviation: GFR, glomerular filtration rate. ^a In all type 2 diabetic patients at the time of diagnosis and type 1 diabetic patients who have diabetes for ≥5 y and during pregnancy.			

decrease in the occurrence and progression of retinopathy, nephropathy, and neuropathy has been demonstrated by observational and randomized studies.^{16,34} These outcomes support the current American Diabetes Association (ADA) recommendations for a goal hemoglobin A_{1c} of <7%.³⁵ However, the reduction of macrovascular complications from glycemic control alone has not been as well established. The United Kingdom Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) trials have also demonstrated “metabolic memory,” by improved glycemic control having a decreased risk of CV events in long-term follow-up.^{16,17} Other trials, on the other hand, have failed to show a reduction in CV risk.^{36–39} Interestingly, reductions of hyperglycemia in type 1 diabetes has shown a decreased long-term risk of the development of hypertension.⁴⁰

The rational approach to type 1 diabetes is an optimized insulin replacement regimen that includes basal and bolus elements. Because of its complex pathophysiology, type 2 diabetes management often requires the use of multiple medications on a background of lifestyle modification. As much as possible, drug combinations should be selected for their efficacy, complementary mechanisms of action, ancillary benefits (especially on CV risk factors),

safety, and tolerability. The most widely used oral agents (metformin, sulfonylureas, thiazolidinediones) have similar glucose-lowering effects (approximately 1% decrease in hemoglobin A_{1c}) at equivalent doses. However, these agents differ with regard to propensity for hypoglycemia, weight gain, fluid retention, and CVD risk. There should be no reservation in adding insulin to the regimen, if glycemic control on oral agents remains suboptimal. Insulin can be started initially as a bedtime basal dose, but, eventually, many patients will require multiple injections of short- and longer-acting insulin preparations for optimal control.

Pharmacologic Targeting of BP Control

Optimization of blood pressure (BP) has been well demonstrated to improve risks of microvascular and macrovascular disease. Several randomized, prospective trials have shown a similar or even greater cardioprotective benefit from BP reduction in patients with diabetes compared with those without.^{41–43} In the UKPDS study, a 10-mm Hg drop in systolic BP reduced the risk of all diabetic complications (24%), retinopathy (34%), stroke (44%), heart failure (56%), and diabetes-related death (32%).⁴⁰ Moreover, the diabetes subgroup (n= 1501) of the Hypertension Optimal Treatment (HOT) study, whose target diastolic BP was ≤80 mm Hg, experienced a 50% reduction in the risk of CVD events compared

Table II. Interventions for Macrovascular Risk Reduction		
RISK FACTOR	GOAL	REFERENCES
Smoking	Cessation, using counseling or medications	25 and 49
Obesity	Weight reduction by: Exercise: 30–60 min of moderate intensity aerobic exercise at least 3 times per week Diet: Fat <30% total calories with <7% saturated fat and <1% trans fat; sodium restriction	51
Hypertension	Blood pressure of <130/80 mm Hg	43, 44, 48, 52 and 53
Dyslipidemia	TG <150 mg/dL High-risk patients: LDL <70 mg/dL Non-HDL <100 mg/dL Apo B <80 mg/dL Non-high-risk patients: LDL <100 mg/dL Non-HDL <130 mg/dL Apo B <90 mg/dL	58–67
Hyperglycemia	Hemoglobin A _{1c} <7%	16 and 17
Hypercoagulability/ dysfibrinolysis	Aspirin primary prevention in high-risk patients ^a Secondary prevention in patients with cardiovascular disease	68
Inflammation	High-sensitivity C-reactive protein <2 mg/L ^b	69
Abbreviations: Apo B, apolipoprotein B; LDL, low-density lipoprotein; non-HDL, non-high-density lipoprotein; TG, triglycerides. ^a Women older than 60 years and men older than 50 years with major risk factors (smoking, hypertension, dyslipidemia, family history of premature cardiovascular disease, albuminuria). ^b Emerging nontraditional target.		

with those with a diastolic BP target of ≤ 90 mm Hg.⁴⁴ Although the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial did not show a significant risk reduction in composite CVD following intensive BP control, a systolic BP <120 mm Hg (compared with 140 mm Hg) did decrease the incidence of stroke by 40%.⁴⁵ Based on the available data, the currently recommended target for BP control in patients with diabetes is <130/80 mmHg.

With regard to selection of antihypertensive agents, the UKPDS, the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), and a meta-analysis by the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) failed to show any consistent CVD benefit of one class of drugs over others when given as single agents for the treatment of hypertension in diabetic and nondiabetic patients.^{40,45} In contrast, more recent studies have shown significant decreases in microvascular and macrovascular complications, CVD, and mortality in patients with diabetes and hypertension treated with regimens that contain angiotensin inhibitors.^{46,47} There is reasonable consensus that angiotensin-converting enzyme inhibitors and receptor blockers are appropriate first-line treatment for hypertension in diabetic patients because of the CVD

benefits shown in some studies and their proven renoprotective effects.

Emphasizing Lifestyle Modification

All patients should be counseled on the importance of lifestyle modification. The Diabetes Prevention Program (DPP) assessed the effects of intensive lifestyle intervention, metformin, and placebo on CV risk factors. The DPP intensive lifestyle intervention consisted of a weight reduction of at least 7% of initial body weight through consumption of a healthy low-calorie, low-fat diet and physical activity of moderate intensity for at least 150 min/wk. This intensive lifestyle intervention alone proved to be better at decreasing BP and improving dyslipidemia, which are both risk factors for CVD, than metformin or placebo.⁴⁸ Therefore, it is indicated to counsel at-risk patients about the benefits of lifestyle intervention, including counseling on smoking cessation, increased physical activity, and dietary modifications.

Studies have shown that smoking increases the risk of CV death among diabetic patients up to 4-fold, and also increases the risk of dyslipidemia and insulin resistance.^{25,49} Therefore, cessation of smoking should be a key part of patient counseling on

the ongoing risks of tobacco use. At least two active smoking cessation interventions should be recommended during the induction phase to decrease craving. Available options include behavioral counseling, nicotine substitution (gum, patch), and medication (bupropion, varenicline).⁵⁰

Increased physical activity, dietary modification, and weight reduction are effective adjuncts for reduction of cardiometabolic risks. Improvements in insulin action, BP, dyslipidemia, and obesity are all well-known benefits of regular exercise. In addition, conditioning from exercise improves cardiorespiratory fitness and overall longevity.⁵¹ Recommended exercise goals should include 30 to 60 minutes of moderately intense aerobic exercise ≥ 3 per week.

Recommended dietary practices should include caloric restriction, reduction in saturated fats and sodium intake, increase in dietary fiber intake, and optimization of carbohydrate intake. The Mediterranean diet, which is based on high fruit, vegetable, and nut intake, has been shown to improve morbidity, mortality, and CV risks, and reverse components of the metabolic syndrome.^{52,53} One distinct feature of hypertension in patients with diabetes (compared with nondiabetic patients) is the associated tendency to sodium retention due to increased renal sodium reabsorption and decreased excretion.^{54,55} Thus, sodium restriction (1500 mg/d) is a particularly important intervention in patients with hypertension and diabetes. The pathophysiology of salt-sensitive hypertension in diabetes also suggests that investigation of the natriuretic system could provide novel insights in such patients.⁵⁶

CONCLUSIONS

Patients with diabetes and hypertension are at an increased risk of macrovascular and microvascular complications. Targeting multiple risk factors is essential in preventing and slowing the progression of these complications. Optimization of glycemic, lipid, and BP control has been demonstrated to improve patient outcomes. The benefits of optimal treatment of dyslipidemia with statin drugs can become evident within months in high-risk patients, whereas significant CVD risk reduction from control of hyperglycemia and hypertension evolves over several years. It is therefore imperative to implement a dedicated approach that emphasizes primary and secondary preventive practices and sustained control of multiple risk factors in patients with hypertension and diabetes. In particular, all patients should be educated on the importance of smoking cessation, dietary modification, and regular physical activity. A multifactorial approach (Table II) with concurrent

optimization of glycemic control, dyslipidemia and BP, as done at the Steno Memorial Hospital in Copenhagen, Denmark, produced a sustained beneficial effect (approximately 50% risk reduction) on macrovascular events as well as all-cause mortality.⁵⁷ This underscores the importance of comprehensive management of comorbid risk factors.

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